SYNTHESIS OF 1-SUBSTITUTED 2,5-BISCHLOROMETHYLPYRROLIDINES

S. N. Borodulina, V. G. Tataurov, S. V. Sokolov, and I. Ya. Postovskii

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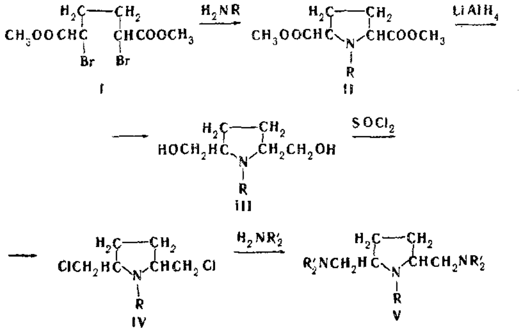
A number of 1-substituted 2, 5-bischloromethylpyrrolidines, cyclic analogs of bis-β-chloroethylamine, have been synthesized. The previously unreported 1-phenyl- and 1-benzyl-2, 5-bis(N-cycloalkylaminomethyl)pyridines and their methiodides have been obtained.

We recently described compounds with possible cytotoxic activity, N-aryl-substituted bis-β-chloroethylamines, in which the α carbon atoms are connected with one another through an ethylene bridge, thanks to which the cytotoxic grouping, by forming part of a pyrrolidine ring, acquires spatial rigidity [1].

To study the influence of steric factors on physiological action it appeared of interest to study new compounds of this type with substituents affecting the basicity of the nitrogen. The synthesis of this type of compounds (**IVa**, **b**, **c**) was carried out by the following route:



a R = C_6H_5, b R = $CH_2C_6H_5$, c R = n-C_5H_{11}, d R = $N(C_2H_5)_2$, e R = piperidinyl; NR'_2 = pyrrolidinyl, piperidinyl, morpholinyl, hexamethyleneiminyl.

The formation of the diesters of the 2,5-pyrrolidinedicarboxylic acids **IIa–e** and their reduction to the corresponding bishydroxymethyl derivatives **IIIa–e** took place with good yields. When the latter compounds were heated with thionyl chloride, individual products, the 2, 5-bischloromethyl derivatives, were obtained only in the case of R = benzyl and amyl. In those cases where R was a diethylamine or piperidine residue, i.e., when a hydrazine grouping (with N' in the ring) was present, heating with thionyl chloride led to pronounced resinification and it was impossible to isolate individual products. When the reaction was carried out in the cold, the starting materials **IIId** and **e** were recovered.

The presence of mobile chlorine atoms in the 2,5-bischloromethylpyrrolidine derivatives makes it possible to obtain numerous compounds from them. Thus, by the reaction of the chlorides **IVa** and **b** with cycloalkylamines, we obtained the triamines **Va** and **b** (table) in the form of viscous uncrystallizable oils. Only 1-phenyl-2,5-bis(N-pyrrolidinomethyl)pyrrolidine crystallized after vacuum distillation and prolonged standing in the cold. All the triamines were characterized in the form of their crystalline picrates*.

On being heated with methyl iodide, the 1-phenyl-substituted triamines gave diiodomethiodides. This type of tetra-substituted pyrrolidine derivative may be of particular interest for testing their physiological activity.

The reaction of 1-benzyl-2,5-bis(N-cycloalkylaminomethyl)pyrrolidines with methyl iodide takes place in a peculiar fashion. When the reaction is carried out in the cold with two moles of methyl iodide, dimethiodides are formed, but when an attempt was made to obtain trimethiodides by heating with an excess of methyl iodide, the benzyl residue was partially replaced by a methyl residue (analogous cases are known in the literature [2]).

EXPERIMENTAL

1-Amyl-2, 5-bismethoxycarbonylpyrroline (IIc). Sixty grams (0.18 mole) of dimethyl meso-α, α'-dibromoadipate (**I**), mp 75–76° C (literature mp 73.5–74° C [3]) was mixed with 47.2 g (0.54 mole) of n-amylamine and 0.5 g of potassium iodide. After the end of the reaction taking place with a rise in temperature, the mixture was heated in the boiling water bath for 2 hr. Then it was cooled, dissolved in 200 ml of water, and extracted with ether. The ethereal extract was washed with 15–20% hydrochloric acid. The acid extracts were neutralized with saturated sodium carbonate solution to a weakly alkaline reaction and extracted with ether. The extracts were over $MgSO_4$, the ether was driven off, and the residue was distilled in vacuum. Faintly yellowish oil with bp 130–131° C (3 mm); d_4^{20} 1.046; n_D^{20} 1.480. Yield 40%. Found, %: N 5.47; MR_D 69.89. Calculated for $C_{13}H_{23}NO_4$, %: N 5.45; MR_D 68.88.

1-Amyl-2, 5-bisethoxycarbonylpyrrolidine, faintly yellowish oil with bp 141–142° C (2 mm), d_4^{20} 1.040, n_D^{20} 1.452. Yield 60–65%. Found, %: N 5.28; MR_D 76.97. Calculated for $C_{15}H_{27}NO_4$, %: N 4.91; MR_D 76.25.

1-Diethylamino-2, 5-bismethoxycarbonylpyrrolidine (IId). A mixture of 60 g (0.18 mole) of **I**, 47.7 g (0.54 mole) of unsymmetrical diethylhydrazine, and 0.5 g of potassium iodide was gently heated until the reaction started. To complete the reaction, the mixture was heated in the water bath for 2 hr. The subsequent treatment was as described above. Light yellow oil with mp 108–110° C (1 mm). Yield 44%. Found, %: N 10.50. Calculated for $C_{12}H_{22}NO_4$, %: N 10.58.

1-Piperidinyl-2, 5-bismethoxycarbonylpyrrolidine (IIe) was obtained by the above-described method with a yield of 20%. Light yellow oil with bp 118–121° C (1 mm), d_4^{20} 1.131, n_D^{20} 1.481. Found, %: N 10.54; MR_D 70.80. Calculated for $C_{13}H_{22}N_2O_4$, %: N 10.37: MR_D 68.02.

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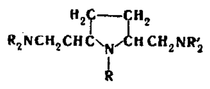
*The 1-phenyl substituted triamines gave dipicrates with picric acid. Because of the higher basicity of the nitrogen atom attached to the benzyl residue, the 1-benzyl-substituted triamines gave tripicrates.

1-Substituted 2,5-Bis(N-cycloalkylaminomethyl)pyrrolidines



Compound	R	NR$_2'$	Bp, °C (pressure, mm)	Empirical formula	N, %		Picrates*			Dimethiodides		
					found	calculated	mp, °C	N, %		decomp. p., °C	N, %	
								found	calculated		found	calculated
Va	Phenyl	Pyrrolidinyl**	190—196 (1—1.5)	$C_{20}H_{31}N_3$	13.55[a]	13.40	209—210	16.25	16.33	110—112	7.23[d]	7.03
	Phenyl	Piperidinyl	217—220 (5)	$C_{22}H_{35}N_3$	12.62	12.30	210—211	15.75	15.76	112—115	6.62	6.72
	Phenyl	Morpholinyl	220—235 (3)	$C_{20}H_{31}N_3O_2$	11.92	12.86	212—213	15.61	15.69	114—115	6.19[e]	6.68
	Phenyl	Hexamethyleneiminyl	237—240 (6)	$C_{24}H_{39}N_3$	10.92[b]	11.37	172—173	15.04	15.23	145—150	6.98	6.43
Vb	Benzyl	Pyrrolidinyl**	199—201 (1)	$C_{21}H_{33}N_3$	13.20	12.83	155—157	16.20	16.54	75—77	6.95[f]	6.87
	Benzyl	Piperidinyl	193—196 (3)	$C_{23}H_{37}N_3$	—	—	164—165	16.00	16.11	130—135	6.40	6.60
	Benzyl	Morpholinyl	212—215 (1)	$C_{21}H_{33}N_3O_2$	11.73[c]	11.75	203—205	16.19	16.01	125—127	6.76	6.53
	Benzyl	Hexamethyleneiminyl	197—200 (3)	$C_{25}H_{31}N_3$	—	—	154—155	14.62	14.35	87—90	5.69	5.47

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*Compound Va was isolated in the form of dipicrates and compound Vb in the form of tripicrates.

**Mp 65–68° C.

[a] Found: C 77.04, H 9.64%. Calculated: C 76.63, H 9.97%. [b] Found: C 76.91, H 9.95%. Calculated: C 77.01, H 10.16%. [c] Found: C 69.56. H 9.27%. Calculated: C 70.02, H 9.26%. [d] Found: I 43.15%. Calculated: I 42.49%. [e] Found: I 38.47%. Calculated: I 38.83%. [f] Found: C 45.40, H 6.25, I 41.62%. Calculated: C 45.18, H 6.39, I 41.60%.

1-Amyl-2, 5-bishydroxymethylpyrrolidine (IIIc). With cooling and stirring, a solution of 13 g (0.05 mole) of the ester **IIc** in 30 ml of ether was added dropwise to 4.2 g (0.1 mole) of $LiAlH_4$ in 210 ml of anhydrous ether. The mixture was boiled for 12 hr, cooled, and treated with 100 ml of water. Stirring was continued for 1 hr. The ether was separated off and the residue was extracted twice with ether. The combined ethereal extracts were dried over $MgSO_4$. After the ether had been driven off, the residue was distilled in vacuum. Colorless very viscous oil, with bp 162–163° C (6 mm), d_4^{20} 1.077, n_D^{20} 1.480. Yield 75–80%. Found, %: C 65.78; H 11.45; N 6.48; MR_D 53.10. Calculated for $C_{11}H_{23}NO_2$, %: C 65.67; H 11.44; N 6.96; MR_D 51.59.

1-Diethylamino-2, 5-bishydroxymethylpyrrolidine (IIId) was obtained by the method described above with a yield of 70%. Colorless viscous oil with bp 154–156° C (5 mm), mp 69–70° C. Found, %: C 59.37; H 11.03; N 14.00. Calculated for $C_{10}H_{22}N_2O_2$, %: C 59.37, H 10.96; N 13.85.

1-Piperidinyl-2, 5-bishydroxymethylpyrrolidine (IIe) was obtained with a yield of 90%. Colorless very viscous oil with bp 164–166° C (3 mm). Found, %: N 13.00. Calculated for $C_{11}H_{22}N_2O_2$, %: N 13.08.

1-Amyl-2, 5-bischloromethylpyrrolidine (IVc). Gaseous HCl was passed into a solution of 3.51 g (0.017 mole) of compound **IIIc** in 20 ml of anhydrous ether. The ether was driven off and the residue was treated with 30 ml of anhydrous chloroform and 18 ml of thionyl chloride. The mixture was boiled for 2.5 hr. The solvent and the excess of thionyl chloride were distilled off in vacuum at a bath temperature of 40° C. The residue was treated with 15 ml of anhydrous benzene, and this was also distilled off. Then the residue was washed with heptane and crystallized from acetone. Colorless lustrous prisms with mp 153–154° C. Yield 55–60%. Found, %: Cl 38.48; N 5.23. Calculated for $C_{11}H_{21}Cl_2N \cdot HCl$, %: Cl 38.75; N 5.10.

1-Phenyl-2, 5-bischloromethylpyrrolidine (IVa) was obtained by the method that we have described previously [1].

1-Benzyl-2, 5-bischloromethylpyrrolidine (IVb) with mp 158–159° C (literature mp 153–156° C) was obtained with a yield of 75–80% as described in the literature [4, 5].

1-Phenyl-2, 5-bis(N-cycloalkylaminomethyl)pyrrolidines (Va). A mixture of 2.44g (0.01 mole) of compound **IVa**, 2.8 g (0.02 mole) of anhydrous potassium carbonate, and 0.02 mole of a cycloalkylamine in 50 ml of anhydrous ethanol was boiled for 30 hr. Then it was cooled and filtered and the ethanol was distilled off in vacuum. The residue was suspended in 100 ml of water, and sufficient concentrated HCl to dissolve it completely was added. Activated carbon was added to the acid solution with heating and it was then filtered, cooled with ice, neutralized with 30% NaOH, and extracted with ether. The ethereal extracts were dried with KOH. The ether was distilled off and the residue was distilled in vacuum. Faintly yellowish viscous oils crystallizing on prolonged standing, with the exception of 1-phenyl-2, 5-bis(N-pyrrolidinomethyl)pyrrolidine. Yield 60–65%. The results of elementary analysis and bps and mps are given in the table.

Dipicrates, bright yellow crystalline substances (from 50% ethanol).

Dimethiodides, slightly yellowish hygroscopic microcrystalline substances not having sharp melting points. They were recrystallized from butanol.

1-Benzyl-2, 5-bis(N-cycloalkylaminomethyl)pyrrolidines (Vb). A mixture of 2.94 g (0.01 mole) of the hydrochloride of compound IVb, 4.2 g (0.03 mole) of anhydrous potassium carbonate, and 0.02 mole of a cycloalkylamine in 50 ml of anhydrous ethanol was boiled for 30 hr. Then the mixture was treated as described above. Yields 60–65%.

Tripicrates, bright yellow substances (from 50% ethanol).

The dimethiodides were obtained by mixing ethereal solutions of 1 mole of 1-benzyltriamine and 2 moles of methyl iodide at room temperature. Faintly yellowish hygroscopic microcrystalline substances (from butanol) (see table).

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Kirov Urals Polytechnic Institute,
Sverdlovsk